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EXAMINER: K

HM32/1026

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | 8 |

**DATE MAILED:** 10/26/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8-4-98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 7-34 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 7-34 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892 (includes reference filed 8/4/98 by applicant, without PTO1449)
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

**--SEE OFFICE ACTION ON THE FOLLOWING PAGES--**

*CHANGE IN ART UNIT*

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1641**.

*AMENDMENT ENTRY*

The AMENDMENT AND REQUEST FOR RECONSIDERATION filed August 4, 1998 (paper no. 6) is acknowledged and has been entered. Claims 1-6 have been cancelled. Claims 7-34 have been added. Claims 7-34 are pending.

*ABSTRACT*

The abstract of the disclosure is objected to because it fails to indicate that the two antibodies are in different forms, i.e. a solid phase one immobilized on an insoluble carrier and a liquid phase one. Correction is required. See MPEP § 608.01(b).

*INFORMALITIES*

The disclosure is objected to because of the following informalities: abbreviations should be fully explained the first time they are used to avoid confusion. Appropriate correction is required.

*PRIOR CITATION OF TITLE 35 SECTIONS*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

*AGGLUTINATION DEFINED*

Agglutination is

> [t]he combination of soluble antibody with particulate antigens in an aqueous medium containing electrolyte, such as erythrocytes, latex particles bearing antigen or bacterial cells to form an aggregate which may be viewed either microscopically or macroscopically. If antibody is linked to insoluble beads or particles, they may be agglutinated by soluble antigen by reverse agglutination. Agglutination is the basis for multiple serological reactions including blood grouping, diagnosis of infectious diseases, rheumatoid arthritis (RA) test, etc. To carry out an agglutination reaction, serial dilutions of antibody are prepared, and a constant quantity of particulate antigen is added to each antibody dilution. Red blood cells may serve as carriers for adsorbed antigen, e.g. tanned red cell or bis-diazotized red cell technique. Like precipitation, agglutination is a secondary manifestation of antigen-antibody interaction. As specific antibody crosslinks particulate antigens, aggregates form that become macroscopically visible and settle out of suspension. Thus, the agglutination reaction has a sensitivity 10 to 500 times greater than that of the preciptin test with respect to antibody detection. (see Cruse et al., ILLUSTRATED DICTIONARY OF IMMUNOLOGY, CRC Press, Boca Raton, 1995).

***NON-ART BASED REJECTIONS***

Claims 7-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims fail to recite clear, distinct and positive method steps.

Claims 7 and 21 are confusing. On the one hand, formation of an agglutinate implies that the claimed immunoassays are agglutination assays. See also claims 8 and 22; as well as the definition of the insoluble carrier in claims 12-15 and 26-29. On the other hand, the method steps might be broadly interpreted as reading on optical measurement of the mass of immunocomplexes formed on the surface of a waveguide. Therefore, it is suggested that the preambles of claims 7

and 21 be amended to recite --An agglutination immunoassay--; and, that --particle-- be added after "insoluble carrier" in claims 7 and 21 (with corresponding amendments to dependent claims 12-15 and 26-29 for proper antecedent basis).

Claims 7 and 21 are unclear by implying, rather than positively stating, that at least one of the two antibodies has at least two binding sites for the target antigen, so that cross-linking or agglutination can occur. It is unclear whether the first and the second binding sites on the antigen are the same or different; and, if they are the same, are they spatially distinct so that both the first and second antibodies can simultaneously bind to the antigen. (See e.g. paragraph bridging pages 4-5 of the specification.)

Claims 7 and 21 are vague and indefinite in reciting "optically measuring the amount of the agglutinate". It is unclear what is being measured and correlated to detection of the antigen. Indeed, claims 7 and 21 fail to recite a method step of detecting the target antigen in the sample as is proscribed in the claims' preamble. It is suggested that language such as --optically measuring the rate of formation of said agglutinate to determine the presence or amount of the antigen in the sample--, or equivalent, such as the change in absorbance over a defined time period, be used. See also claims 8 and 22 where "measuring decreasing light transmission" also suggests a *rate* measurement is being used. (See e.g. paragraph bridging pages 4-5 and page 11, paragraph 1of the specification.)

In claims 8 and 22, insert --the-- before "formation" for proper antecedent basis.

It is unclear how claims 12 and 26 further limit claims 7 and 21 since claims 12 and 16 appear to recite all possible insoluble carriers. It is unclear what is *not* covered by these claims.

Claims 17 and 31 recite an improper Markush group with overlapping members; and, contain spelling errors. Claims 17 and 31 are non-idiomatic and of indeterminate scope in reciting "DNA-binding protein factors" as it is unclear what defines such factors.

Claims 19 and 33 are confusing in defining an immune-reaction accelerating component which is **not** present in the sample of claims 18 and 32, respectively; and, as such, claims 19 and 33 also fail to further limit claims 18 and 32.

Claims 7-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for agglutination immunoassays wherein a particle immobilized antibody and a liquid phase "free" antibody bind to different binding sites on the antigen, does not reasonably provide enablement for immunoassays using any type of insoluble carrier for immobilizing antibody and combination of antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Agglutinate formation requires crosslinking of the antigen-antibody complexes; and, thus, use of paired antibodies which bind to different binding sites on the antigen. Based upon the instant specification, one of ordinary skill in the art would not know how else to perform the claimed methods. (Also note the specification teaches away from the two antibodies competing for target antigen in the paragraph bridging pages 3-4.)

***ART BASED REJECTIONS***

*Based on Strahilevitz*

Claims 7, 10-13 and 18-19 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Strahilevitz (US 4,375,414, **newly cited**).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Strahilevitz (US 4,375,414, **newly cited**).

Strahilevitz describes an agglutination immunoassay for determining a hapten, such as a drug or a steroid, in a sample wherein sample is mixed with an agglutinable carrier-bound anti-hapten antibody in suspension and then mixed with a free anti-hapten antibody. If sample contains above a minimal amount of the free hapten, agglutination results. Although erythrocytes are the prefered carrier, other materials, such as latex or other particles, are also useful. (col. 3, lines 15-37). This method has the advantage of indicating the presence of hapten by hemagglutination rather than by hemagglutination inhibition. (col. 7, Example 5). Thus, as to claims 7, 10-13 and 18-19 Strahilevitz describes the claimed invention. As to claim 17 while Strahilevitz describes haptens such as drugs and steroids like estrone, Strahilevitz differs in failing to disclose other haptens as explicitly claimed in the recited Markush group. However, it would have been obvious to one of ordinary skill in the art to adapt the methods and reagents of Strahilevitz to other haptens of known medical importance to obtain diagnostic and therapeutic information thereof.

*Based on EP '285 A2*

Claims 21-27 and 29-34 rejected under 35 U.S.C. 102(b) as being clearly anticipated by BOEHRINGER MANNHEIM GMBH (EP 617 285 A2, **English translation of IDS reference AL which replaces Derwent Abstract Accession No. 94-295892/199437**).

First off, applicant is thanked for supplying the English translation of EP '285.

BOEHRINGER MANNHEIM GMBH (EP 617 285 A2), hereinafter EP '285 A2, describes an agglutination immunoassay for determining analyte by binding analyte to a receptor R1 which is immobilized on a particulate carrier and a soluble receptor R2 (i.e. free antibody) which is specific for analyte and has at least two binding sites for the analyte (page 3, ¶3). R1 and R2 may independently be monoclonal antibodies, polyclonal antibodies or antibody fragments (page 3, ¶¶ 5 and 7). Preferably, R2 recognizes a different epitope on the analyte than the immobilized R1, which advantageously yields a somewhat higher sensitivity in the ascending branch of the Heidelberger Curve, a ~~shit~~ shift of the maximum to a higher analyte concentration, and a substantially slower descent of the Heidelberger Curve with increase of analyte concentration being achieved (page 4, ¶3). Preferably, the reaction mixture also contains an accelerator, such as 6 kD polyethylene glycol (page 5, ¶2). The particulate carrier is any desired particulate carrier that is known in the state of the art for performing agglutination tests, preferably latex particles, metal sols and liposomes, with sizes ranging from 10 to 500 nm (page 5, ¶3). The analyte is any substance that has at least two epitopes, preferably proteins or human chorionic gonadotropin (page 5, ¶5). Analyte concentration can be determined with suitable equipment either by nephelometry or by turbidimetry by comparison to a standard curve of known analyte

concentrations (page 5, ¶6). The Test Procedure on page 7, describes a *sequential* method wherein sample and soluble antibody are stirred and incubated for 5 minutes before immobilized antibody is added.

Applicant argues EP '285 A2 is a simultaneous, not sequential, method.

The Test Procedure on page 7 reads as follows:

> The Fab'-coated latex was produced by mixing SA latex with the Fab' antibody fragments (hCG)-1 and -2 in the latex buffer system. The final concentration of SA latex in the buffer was 0.1% (wt./vol.) and that of the Fab' fragments was 0.4 µg/ml. The $F(ab')_2$ antibody fragments (hCG)-3 and (hCG)-4 were added to the reaction buffer at different concentrations. The experiment was carried out on a Hitachi 717 Analyzer at 37° C. 20 µl of standard solution was pipetted into a cuvette, immediatedly after which 330 µl of the **reaction buffer containing the soluble antibody** fragment (hCG)-3 or (hCG)-4 at various concentrations was added. After stirring, **the mixture was incubated for 5 minutes and** 50 µl of **latex solution was *then* added**. The mixture was stirred again and incubated for 5 minutes. The course of the reaction was followed by measuring the change of absorption at 340 nm. (emphasis added)

Thus, insofar as EP '285 A2 discloses *sequential* contact with the immobilized antibody *5 minutes after* the soluble antibody was contacted with the sample, this argument is not persuasive.

Applicant argues the purpose of EP '285 A2 is limiting or preventing the hook effect in the assay by simultaneously contacting the analyte with R1 and R2. The skilled artisan would not have expected sequential contact with R1 and R2 to reduce or prevent the hook effect; and, therefore, would have no reason to conduct the assay in this manner.

This argument is not persuasive because EP '285 A2 does suggest *sequential* contact as stated *supra*; and, because applicant has not provided an reasoned explanation for his conclusion that *sequential* contact would have been expected to be *inoperative*.

*Based on Cragle et al.*

Claims 7-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cragle et al. (WO 85/02258) taken together with Strahilevitz (US 4,375,414, **newly cited**) and BOEHRINGER MANNHEIM GMBH (EP 617 285 A2).

Strahilvetz and EP '285 A2 have been described *supra*.

Cragle et al. describes an improved nephelometric immunoassay for an antigen in a fluid sample comprising contacting the sample with both a solid phase antibody and liquid phase antibody therefore and measuring the amount of formed complexes, i.e. agglutinates, wherein the hook effect is avoided. (See especially the "improved direct nephelometric immunoassay" descriptions on page 7, ¶2, which contrary to applicant's arguments does NOT require use of a labeled antibody.) (See also page 9, ¶6 (antibodies are independently monoclonal or polyclonal antibodies.) Cragle et al. differs in failing to disclose *sequential* contact with the two antibodies; use of a calibration curve; all of the specifically claimed carrier types; all of the specifically claimed analytes; and, use of an immune-reaction accelerating compound, such as 6 kD polyethylene glycol.

It would have been obvious to modify the methods and reagents of Cragle et al. by contacting sample with the solid phase and liquid phase antibodies *sequentially* as suggested by

Strahilevitz (solid phase antibody first followed by liquid phase antibody) or EP '285 A2 (liquid phase antibody first followed by solid phase antibody) to directly indicate analyte (Strahilevitz) or or optimize sensitivity and range (EP '285 A2); to use a calibration curve as suggested by EP '285 A2 to obtain quantitative results; to use any solid phase carrier typically used in agglutination assays, as suggested by EP '285 A2 for the same intended purpose; to determine any analyte of medical, economic, etc. importance known to be amenable to agglutination assays, including steroids, proteins, etc. as suggested by all three references; and to use a known immune-reaction accelerating compound, such as 6 kD polyethylene glycol, as suggested by EP '285 A2 to save time.

## *CLOSING*

In conclusion, applicant's amendments and arguments filed August 4, 1998 have been fully considered but are not deemed convincing of patentability for the above reasons and reasons of record.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Craig (US 5,492,841) discloses a particle based agglutination assay wherein the change in turbidity caused by particle agglutination or its inhibition is measured. The reaction can be performed by direct competition between the particle reagents and the hapten or by sequential reaction of the hapten with antibody followed by addition of the particle reagent (col. 12, ¶2).

Cruse et al. (ILLUSTRATED DICTIONARY OF IMMUNOLOGY, CRC Press, Boca Raton, 1995, pages 8-9) provides an art-recognized definition of "agglutination."

Soybel et al. (*Clinical Chemistry*, 32 (6):1084-1085, June 1986, Abstract No. 174) describes a sequential latex agglutination inhibition immunoassay.

Tietz (ed.) (TEXTBOOK OF CLINICAL CHEMISTRY, W.B. Saunders Company, Philadelphia, 1986, pages 230-231) provides a generic discussion of agglutination assays, including the use of immune-reaction accelerators.

BOEHRINGER MANNHEIM GMBH (EP 617 285 A2) the English translation of IDS reference AL is being cited on the accompanying PTO-892 because it was supplied by applicant without an accompanying PTO-1449.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Carol A. Spiegel
October 20, 1998